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FOUR SULFONAMIDE AGENTS HAVING PROPERTIES SUITABLE FOR TREATMENT OF DERMAL *STAPHYLOCOCCUS AUREUS* INFECTIONS

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ABSTRACT

The most common bacterial pathogen associated with dermal infections across the world is *Staphylococcus aureus*. Up to 90% of all dermal bacterial events in the Northern Hemisphere are due to *Staphylococcus aureus* (*S. aureus).* This study presents four sulfonamide agents that have been shown to substantially inhibit the growth of *S. aureus* and possess favorable drug-likeness by way of having zero violations of the Rule of 5, which is an excellent indicator of drug like properties. All four sulfonamide agents showed greater that 30% inhibition of *S. aureus* at concentrations as low as 50 micrograms per milliliter. In addition, their molecular properties of molecular weight, polar surface area, and Log P are within the parameters of favorable drug-likeness. The dermal permeability constant, Kp, has been determined for each agent, for further comparison. Numerical values of Kp are expressed in centimeters per hour (cm/hour) and allow the estimation of dermal penetration based on measurement of time. The estimated dermal penetration of each agent over 1, 2, 3, 4, up to 10 hours, is shown graphically for comparison. The use of sulfonamide agents for the treatment of *S. aureus* dermal infections appears to have substantial efficacy.

KEYWORDS: *Staphylococcus aureus*, sulfonamide, antibacterial.

INTRODUCTION

Across the globe, the most common causative pathogen of dermal infections is *Staphylococcus aureus*.[1] The presence of infection is observed clinically in a variety of manifestations and are linked to several toxins produced by *S. aureus*.[1] The appearance of *S. aureus* in dermal infections is highly prolific and irrespective of geographical area, climate, or age of the patient.[1] Sulfonamide drugs are a very important group of synthetic pharmaceutical agents that are applied clinically as broad spectrum antimicrobial drugs, for treatment for both human and animal bacterial infections.[2] Sulfonamide drugs are compounds having - SO_2NH- groups (or - SO_2NH_2- groups).[2] Sulfonamide drugs commonly have aromatic or heterocyclic rings.[2] In animals, sulfonamide drugs are used to treat gastrointestinal and/or respiratory tract infections in livestock.[2] Sulfonamide drugs are not considered to be biodegradable and in high doses may induce allergic reactions.[2] Human skin is considered the largest organ of the body and generally, in adults, it has an area of 2 square metres and weighs about 5 kilograms.[3] The thickness of the skin varies from 0.5 mm thick on the eyelids to 4.0 mm thick on the heels of feet.[3] Functions of skin include the following: 1) Protection, it protects against UV light, mechanical, thermal and chemical stresses, dehydration and invasion by micro-organisms, 2) Sensation: skin has receptors that sense touch, pressure, pain and temperature, 3) Thermoregulation, various features of the skin are involved in regulating temperature of the body. There are three layers of skin: The epidermis: a thin outer portion, The dermis: a thicker inner portion, and the hypodermis.[3,4]

The dermal permeability constant, Kp, is highly utilized and considered highly accurate for determining expected penetration and travel of various compounds within the dermal layers.[5] The rate of travel is determined in centimeters per hour (cm/hour), with Kp considered the key parameter for dermal absorption.[5]

MATERIALS AND METHODS

Molecular Properties and Molecular Modeling

The numerical values of molecular properties (i.e. Log P, polar surface area, molecular weight) for all agents were determined by heuristic calculation through Molinspiration Chemical Properties Service (Molinspiration Cheminformatics, Nova ulica 61, SK-900 26 Slovensky Grob, Slovak Republic). Molecular structural components was shown and analyzed utilizing ACD ChemSketch Modeling v. 12.01 (Advanced Chemistry Development, 110 Yonge Street, Toronto Ontario, M5C 1T4 Canada, //www.molinspiration.com/services/search.html).

Molinspiration Cheminformatics (//www.molinspiration.com/cgibin/properties), determined molecular properties of Log P, polar surface area (Angstroms^2), molecular weight, number of nitrogen, oxygen, amine groups, and hydroxyl groups (for determination of hydrogen bond donors and hydrogen bond acceptors).

The dermal permeability constant, Kp, was determined by DERWIN v 1.42 (U.S. Environmental Protection Agency, copyright). From values of Kp determined by DERWIN, the relative travel within dermal tissue can be estimated. All statistical calculations were accomplished using PAST v. 2.15 (copyright Hammer and Harper 1999-2012), Oyvind Hammer, D.A.T. Harper (April 2012).

RESULTS AND DISCUSSION

Sulfonamide drugs are compounds having -SO_2NH- groups (or -SO_2NH_2- groups).[2] Sulfonamide drugs commonly have aromatic or heterocyclic rings.[2] The sum value of the polar surface area (PSA) of a pharmaceutical is the total of surface area contribution of electronegative atoms such as oxygen, fluorine, and nitrogen.[5] The PSA value is a key parameter for the drugs absorption and permeability.[5] Values of PSA influences the efficacy of a drug to be absorped in the gastrointestinal tract, penetrate through biological membranes, and penetrate the blood-brain barrier. A high value in PSA will decrease lipid solubility, decrease permeability, and decrease oral bioavailability. In general, polar molecules are poorly absorbed through dermal layers, whereas, nonpolar molecules become more readily absorbed.[5] The major routes of pharmaceutical diffusion through the skin is: (1) Intercellular (movement of the drug around and past dermal cells); (2) Transcellular (the movement of the drug passing through dermal cells); (3) Transappendageal (drug delivery via sweat glands or hair follicles within the skin).[5]

All four of sulfonamide agents of this study have molecular structures shown in Fig. 1. The IUPAC names and SMILES notation (Simplified Molecular Input Line Entry System) are also shown. The synthesis of the agents and testing for inhibition of *Staphylococcus aureus* bacterial growth, was accomplished, and has been shown in previous studies by Bartzatt, et al.[6,7] This present study examines the efficacy of applying these sulfonamide agents as agents for the clinical use of inhibiting *Staphylococcus aureus* dermal infections. All four agents, shown in Fig.1, have two aromatic rings and the definitive (-SO_2NH-) group. That portion being common to all four agents, then the substituents on the aromatic rings will be important in any comparative variation of molecular properties.

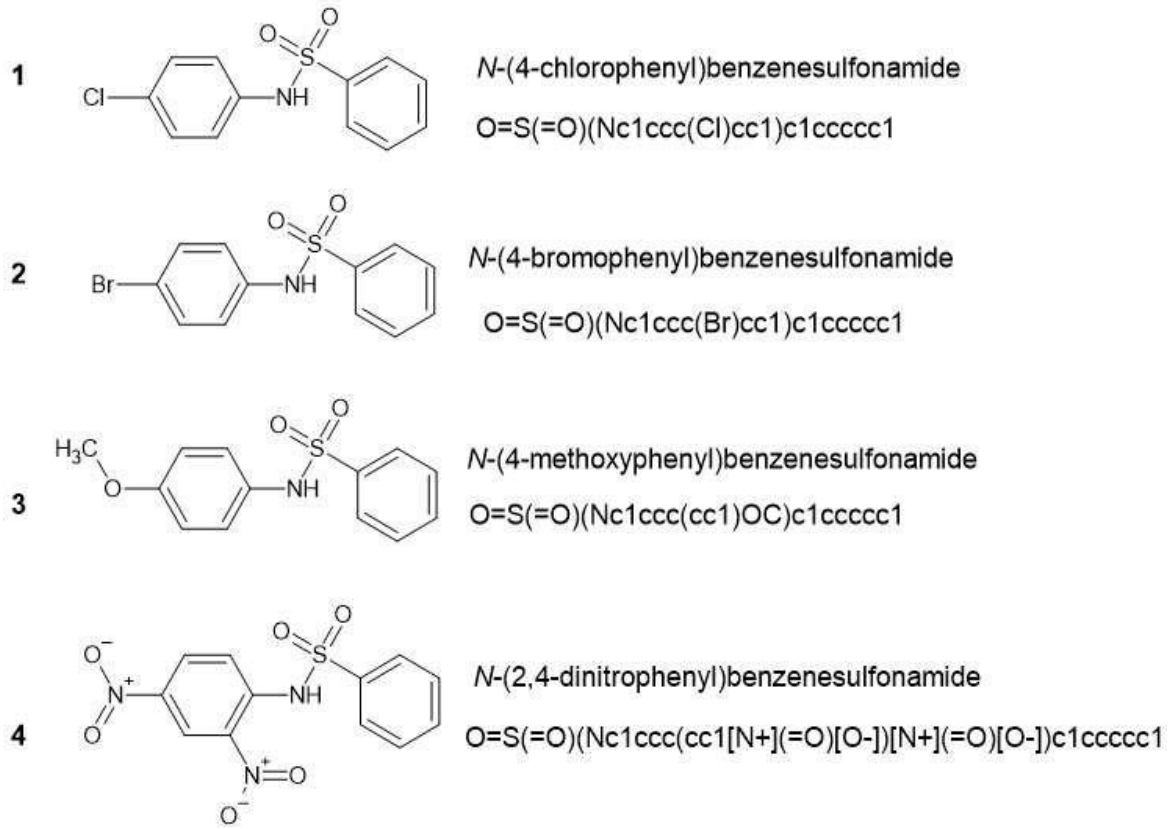

Figure 1: Four sulfonamide agents having molecular structure shown and SMILES designation. Note that all agents have the -SO_2NH- group. All agents have two aromatic rings. Substituents may include halogen atoms of chlorine or bromine (agents 1 and 2). Otherwise a methoxy group (agent 3) or nitro group (agent 4).

The drug-likeness of a potential pharmaceutical is the description of how similar the molecular properties are to successful drugs and how well the match is to screening parameters defining said drugs. A highly successful categorical screening set of drug-likenss parameters is referred to as the Rule of 5.[8] The criteria of the Rule of 5 for favorable drug-likeness, is the following: 1) Not more than 5 hydrogen bond donors; 2) Not more than 10 hydrogen bond acceptors; 3) Formula weight less than 500; 4) Log P less than 5.[8] In the case of the four sulfonamides presented here, all four have zero violations of the Rule of 5, and consequently very favorable drug-likeness.

The absorbed dermal dose rate, as Kp (permeability coefficient), can be determined for pharmaceuticals contingent on the molecular weight (MW) of the drug and the lipid solubility as indicated by values of Log P (or Log Kow).[3,4] This parameter of Kp is generally considered to be accurate and efficacious.[3,4] The algorithm for determination of Kp is as follows:[3]

Log Kp = (0.71)Log P - (0.0061)(MW) - 2.72

Kp = Permeability coefficient

Log P = octanol/water partition coefficient MW = molecular weight

Significanat molecular properties for considering drug-likeness include Log P, molecular weight, polar surface area, and sum of hydrogen bond donors (H-bond donors) and hydrogen bond acceptors (H-bond acceptors), are presented in Table 1. Hydrogen bond donors include -OH and -NHn, whereas hydrogen bond acceptors include oxygen and nitrogen.[8] The molecular weight of all four sulfonamides are below 500 dalton. T)he values of polar surface area range from 40.98 Angstroms^2 (for agent 1 and 2), 49.36 Angstroms^2 (agent 3), to the largest value of 137.82 Angstroms^2 for agent 4. The values of Log P (octanol/water partition coefficient) shows higher lipophilicity for agents 1 and 2, with lowest lipophilicity for agent 4 (agent 3 set between agents 1,2 and 4). The largest permeability coefficent (Kp) values is 00094 cm/hour for agent 1, run to the smallest value of 0.000828 cm/hour for agents 4, which carries two -NO_2 groups. The presence of two -NO_2 groups covalently bonded with agent 4 apparently increases polar surface area, decreases Log P (and decreases lipophilicity), and substantially decreases Kp values in comparison to agents 1, 2, and 3. A similar relationship can be observed for sum of H- bond donors and H-bond acceptors, at 10 for agent 4, when compared to agents 1, 2, and 3.

TABLE 1

Drug	MOLECULAR WEIGHT (grams/mole)	POLAR SURFACE AREA (Angstroms^2)	LOG P	PERMEABILITY COEFFICIENT (cm/hour)	SUM OF H-bond DONORS AND H-bond ACCEPTORS
1	267.7	40.98	3.27	0.0094	4
2	312.2	40.98	3.47	0.00752	4
3	263.3	49.36	2.63	0.00398	5
4	323.3	137.82	2.55	0.000828	10

Previous studies presented by Bartzatt et al. showed the substantial growth inhibition of *Staphylococcus aureus* induced by agents 1, 2, 3, 4.[6,7] The percent growth inhibition of *Staphylococcus aureus* by each agent is presented in Table 2. Notable is a greater than 30% inhibition of *Staphylococcus aureus* by all agents at concentrations as low as 50 microgram/mL. Bacterial growth inhibition was substantial at higher concentrations of agents, to include (microgram/mL): 50, 100, 200, and 400. Clearly, all agents presented here are effective for inhibiting bacterial growth of *Staphylococcus aureus*.

TABLE 2

Concentration (microgram/mL)	Percent Growth Inhibition of Staphylococcus aureus			
	Agent 1	Agent 2	Agent 3	Agent 4
0	0	0	0	0
50	41	46	39	47
100	44	49	40	57
200	45	51	43	63
400	48	57	45	70

Previous studies have shown that molecular polarizability, is considered as an electronic property that has significant influence on chemical-biological interactions.[9] Consequently, molecular polarizability plays a significant role in explaining interactions that occur within the category of Structure Activity Relationships (SAR) and should be considered along with other drug-like properties/descriptors.[9] Other studies have indicated that in order to represent intermolecular interaction energies, particularly for receptor docking studies and flexible molecules, an account must be made for inter- and intra-molecular polarization (and charge transfer effects).[10]

Looking at Table 3, for comparison of Kp, polarizability, and polar surface area; notably the smallest numerical value for Kp (0.000828 cm/hour) also corresponds to the largest polarizability and largest polar surface area. The largest value for Kp (0.0094 cm/hour) corresponds to the smallest polarizability and smallest polar surface area. These observations are consistent with findings of previous studies of percutaneous absorption, ligand and drug receptor interactions.[3,4,5,10] Looking at Table 3, polarizability has high positive correlation (Linear correlation r) with polar surface area at 0.9226. The values of Kp have high positive correlation with Log P values, at 0.8903. The numerical values of Kp have a strong negative correlation with polarizability, at -0.8303.

TABLE 3

Agent	Kp (cm/hour)	Polarizability (x 10^{-24} cm^3)	Polar Surface Area ($Angstroms^2$)
1	0.0094	27.25	40.98
2	0.00752	28.40	40.98
3	0.00398	27.86	49.36
4	0.000828	30.12	137.82

Therefore, all agents 1, 2, 3, 4 show zero violations of Rule of 5 and favorable drug-likeness. Molecular properties for these agents are shown, and previous studies have demonstrated that all four agents substantially inhibit bacterial growth of *Staphylococcus aureus* at concentrations as low as 50 microgram/mL.[6,7]

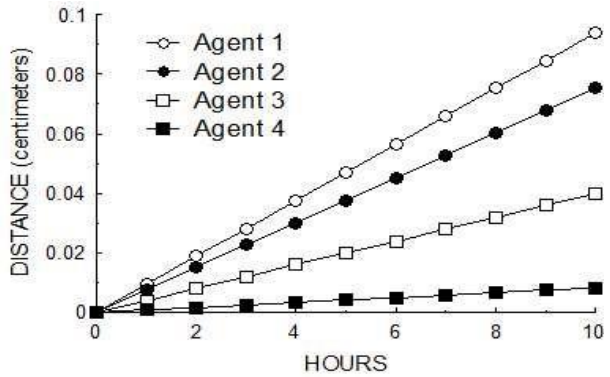

Figure 2: Dermal penetration of agents based on Kp values in cm/hours (see Table 1). Note that agent 1 and 2 have the greatest dermal penetration, with a chlorine substituent (agent 1) or bromine substituent (agent 2). Agent 4 having two nitro groups has much higher polar surface area and slowest dermal penetration per hour. Agent 3 falls between agent 4 and that of agents 1 and 2.

Shown in Fig.2 are the projected values of dermal penetration for agents 1, 2, 3, 4 in centimeters and per hour of exposure, to accomplish percutaneous action. For each agent, the extent or distance of dermal penetration is a linear function to be expressed in centimeter per hours (see Fig.2). Considering the human skin as composed of two layers; the nonvascular epidermis at 0.010 centimeters thick and the highly vascularized dermis ranging from 0.050 centimeters to 0.300 centimeters thick.[4] For the epidermis the outermost layer or stratum corneum is approximately 0.0010 centimeters to 0.0040 centimeters thick and is considered to be the major barrier to absorption into the circulation of agents deposited on the surface of the skin.[4] Below this outer layer is the viable epidermis, a layer of about 0.0050 centimeters to 0.010 centimeters thick.[4]

In less than two hours, agents 1 and 2 will cross past the nonvascular epidermis layer. While agent 3 will cross past this nonvascular epidermis layer in less than three hours. In ten hours, agent 4 will nearly past through the epidermis layer or 80% of the epidermis. In reaching the highly vascularized dermis, all agents will emcompass the blood vessels and capillaries of the skin. The agents will initially pass through the stratum corneum, followed by passage through the deeper epidermis and dermis.[11] Agents reaching the vascularized dermis (i.e. dermal microcirculation) enables systematic absorption of the drug.[11] Transdermal drug delivery has multiple advantages: 1) It is painless; 2) Drugs become available for systematic absorption; 3) Provide a non-invasive

manner of drug administration; 4) Large dermal surface area permits the choice of multiple placement options; 5) Further passage of drug to other tissues.[11] The sulfonamide agents presented in this study, consequently, show potential for effective treatment of dermal infection, and in particular the inhibition of growth of *Staphylococcus aureus*. These agents, and similar agents of their kind, deserve further study and consideration for applications in the treatment of dermal bacterial infection.

CONCLUSION

Across the globe, *Staphylococcus aureus* is the most common causative factor of skin infections. Sulfonamides belong to the synthetic group of antimicrobial drugs and are considered to be a broad spectrum antimicrobial suitable for use in humans and animals. Presented here are four agents previously tested and shown to substantially inhibit the growth of *Staphylococcus aureus*. Common structure features of the four agents are two aromatic rings and the -SO_2NH- group. Agent 1 had the halogen (-Cl) substituent, agent 2 had (-Br) substituent, agent 3 methoxy group (-OCH_3), and agent 4 having two -NO_2 groups. Agent 1 and 2 showed the largest values of Kp and consequently the fastest permeation into skin tissue, and deepest penetration relative to agents 3 and 4. The methoxy substituent on agent 3 induced a greater polar surface area (49.36 A^2) for agent 3 and somewhat smaller Kp value relative to agent 1 and 2. Agent 4 having two -NO_2 groups and much larger polar surface areas (137.82 A^2), resulting in a much smaller Kp value, hence much slower permeation of skin layers. Elucidation of novel sulfonamide agents will provide additional clinically useful drugs for the treatment of *Staphylococcus aureus* infections of the skin.

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